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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,452	10/31/2000	David B. Weiner	UPAP-0404	6483

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/622,452	WEINER ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,9-15,17,18,33-36 and 40-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,9-15,17,18,33-36 and 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/20/06 has been entered. Applicant's amendment and response also received on 1/20/06 has been entered. Claims 20-22 have been canceled and new claims 40-45 have been added. Claims 1-4, 6-7, 9-15, 17-18, 33-36, and 40-45 are currently pending and under examination in the instant application. An action on the merits follows.

The applicant is reminded that the claims under examination, while generic, have been examined in view of the elected subject matter, i.e. plasmids as the nucleic acid, and DR5 as the immunomodulatory protein.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Rejections - 35 USC 112

The rejection of claims 1-4, 6-7, 9-15, 17-18, and 33-36 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained in modified form over pending claims 1-4, 6-7, 9-15, 17-18, 33-36, and 40-45. Applicant's arguments and the Declaration under 37 CFR

1.132 by Dr. Weiner have been fully considered but have not found persuasive in overcoming the instant grounds of rejection set forth below.

In view of applicant's Declaration under 37 CFR. 1.132, the following subject matter is found to be enabled by the specification.

The specification, while being enabling for 1) a method of immunizing a mammal against Influenza comprising co-administering a plasmid DNA encoding Influenza HA and a plasmid encoding DR5 by intramuscular injection and 2) a pharmaceutical composition comprising a plasmid encoding Influenza HA and a plasmid encoding DR5, does not reasonably provide enablement for pharmaceutical compositions comprising a plasmid encoding any immunogen and a plasmid encoding DR5 or for methods of enhancing an immune response or methods of immunizing against any pathogen by administering plasmid(s) encoding an immunogen and DR5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Please note that while claims 1-4, 6, 9-10, 12-15, 17, 40, and 42-43 are composition or pharmaceutical composition claims, they have been included in this rejection based on the disclosed intended use of the compositions for immunizing a host against disease.

In response to the previous grounds of rejection of the claims based on the lack of enabling disclosure provided by the specification for using DR5 as an immunomodulatory protein, the applicant has submitted a declaration under 37 CFR 1.132 by Dr. Weiner which includes a manuscript that demonstrates that the co-administration of a plasmid encoding HIV envelope protein and a plasmid encoding DR5 by intramuscular injection can increase CD8+ T cell responses against the envelope protein. The manuscript further demonstrates that the

intramuscular co-administration of a plasmid encoding Influenza HA and a plasmid encoding DR5 can protect mice against challenge with a lethal dose of Influenza virus. In view of these results that demonstrate that DR5 has immunomodulatory properties in enhancing CD8+ T cell responses, the previous grounds of rejection of the claims has been withdrawn. However, consideration of applicant's declaratory data in conjunction with the teachings of the specification leads to the following new grounds of rejection.

The specification broadly discloses the use of a single plasmid encoding an immunogen and an "immunomodulatory" protein or a combination of a first plasmid encoding an immunogen and a second plasmid encoding an "immunomodulatory protein" for inducing immune responses *in vivo*. The specification generally discloses numerous immunogens and "immunomodulatory" proteins which can be used in the disclosed plasmids and compositions. The immunogens include pathogenic antigens, cancer-associated antigens, and antigens linked to cells associated with autoimmune disease. The specification lists examples of these different types of antigens including HIV or HSV antigens as pathogenic antigens, p53 and ras for cancer-associated antigens, and various T cell receptors as antigens linked to cells associated with autoimmune disease. In all such cases, the specification clearly indicates that the purpose of the invention is to generate antigen specific immune responses against the encoded immunogen in order to treat or prevent the associated disease or infection. In regards to "immunomodulatory" proteins, the specification likewise lists a large number of genes, including the death receptor DR5. The specification, however, does not provide any specific guidance as to particular immunogens to be combined with DR5 or provide any specific guidance concerning the use of DR5 as an immunogen.

At the time of filing, the art taught that DR5 has apoptotic properties (MacFarlane et al. (1997) J. Biol. Chem., Vol. 272 (41), 25417-25420 and Sheridan et al. (1997) Science, Vol. 277, 818-821). The prior art did not teach or suggest that DR5 had an immunomodulatory properties or could enhance T cell, B cell, NK cell or any other immune effector cell function in response to antigen. The specification does not provide any guidance which supplements the knowledge present in the prior art concerning DR5. The specification, while listing DR5 among numerous other proteins identified by the specification as "immunomodulatory", fails to provide any specific description of the activity of DR5, particularly in modulating any type of immune response, or provide any specific guidance for the generation of any type of immune response following administration of plasmids encoding DR5 and an immunogen. While the specification does in fact provide a number of examples of the broader invention relating to the ability of proteins such as ICAM, LFA-1, and GM-CSF to modulate the immune response to model antigens, the specification does not provide any specific guidance for the use of DR5 as an "immunomodulatory" protein.. Further, DR5 is not related structurally or functionally to the immunostimulatory molecules exemplified in the working examples such that a correlation can be made between the activity of the cytokines and chemokines utilized in the working examples and DR5.

While the applicant's Declaration provides evidence that DR5 can act to increase CD8+ T cells to antigen when co-administered to muscle with the antigen in the form of plasmid DNA, the declaratory evidence is not commensurate in scope with the breadth of the instant claims as written. The manuscript provided as Exhibit 1 does not teach or suggest that the co-administration of plasmid encoding DR5 has any effect on B cell responses, or any other immune

effector cell responses other than CD8+ T cell responses. The instant claims are not so limited and read on the enhancement of any type of immune response. Based on the lack of guidance provided by the prior art or the specification concerning the activity of DR5 as an immunomodulatory protein, and the limitation of the declaratory evidence to a showing that DR5 can enhance CD8+ T cell responses, the skilled artisan would not have been able to predict without undue experimentation whether the adjuvant activity of DR5 was capable of affecting B cell, NK cell, or other immune effector cell responses. It is further noted that while the declaratory evidence provided shows the generation of CTL responses against HIV envelope, the manuscript does not correlate the level of CTL generated with any therapeutic effect against HIV infection.

Further, in regards to the generation of therapeutic immune responses, and methods of immunizing against viral infections or cancer, at the time of filing, the skilled artisan did not consider the generation of prophylactic or therapeutic immune responses against pathogens, particularly HIV, or tumor associated antigens using nucleic acid immunization as predictable. The art at the time of filing identifies several factors which significantly affect the generation of immune responses to an antigen which include, genetics, dose or concentration of antigen, and route of antigen administration (Abbas et al. (1996) Nature, Vol. 383, 787-793, and Golding et al. (1994) Am. J. Trop. Med. Hyg., Vol. 50 (4), 33-40). The prior art teaches that the concentration of antigen significantly affects the development of cellular (Th1) versus humoral(Th2) immune responses such that low antigen concentrations preferentially induce Th1 type responses and high concentrations of antigen induce Th2 type responses (Abbas et al., *supra*). A further complicating factor is the genetic background of the infected mammal. The

prior art contains numerous reports which demonstrate the Balb/C mice versus C57Bl/6 mice develop different responses to various pathogens. The nature and route of administration of the antigen is also of concern to the generation of a particular T helper phenotype. Golding et al. teaches that intravenous or intraperitoneal immunization leads to preferential induction of Th1 cells whereas subcutaneous or intramuscular immunization leads to Th2 cells which may be attributable to the participation of various antigen-presenting cells (Golding et al., *supra*). Thus, the art at the time of filing clearly teaches that a significant number of variables affect the generation of specific immune responses which render the generation of a particular type of immune response in any mammal unpredictable for any given antigen.

Furthermore, the strength and nature of the immune response generated by a particular antigen was known at the time of filing to be critical to its ability to successfully protect against infection. A weak immune response, or an immune response that only generates antibodies and no CTL may be insufficient to protect against many pathogens. In the case of pseudorabies virus, Monteil et al. discloses that the immunization of naive one-day-old piglets with a plasmid DNA encoding the gene for the gD glycoprotein induces antibodies which do not protect the piglets from PRV challenge (Monteil et al. (1996) Veterinary Research, Vol. 27 (4-5), page 443, abstract). Yasutomi et al. further teaches that immunization of rhesus monkeys with a live viral vector which encodes the SIV gag protein generates a non-protective CTL response, but fails to generate a humoral immune response despite the presence of MHC class II and antibody binding epitopes in the gag protein (Yasutomi et al. (1995) J. Virol., Vol. 69 (4), page 2279, abstract). In addition, Yasutomi et al. teaches that while boosting vaccinated animals with a gag peptide/liposome complex significantly increases the anti-gag CTL response, it still did not

provide increased protection against SIV challenge (Yasutomi et al., *supra*, abstract). Further, in a review of genetic immunization, Ertl and Zhiang emphasize the critical role of the antigen by stating that, " although any antigens can be delivered by genetic immunization, some proteins upon expression by plasmid vectors remain immunologically silent. The principles that govern success versus failure of genetic immunization with regard to each individual protein remain to be elucidated" (Ertl et al. (1996), Viral Immunology, Vol. 9 (1), page 2, lines 32-35). Erdile et al. further provides a demonstration of difficulties in generating therapeutic CTL against an endogenous cancer antigen. Erdile et al. teaches that administration of a p53 class I peptide and anti-CD40 antibody, while stimulating a detectable CTL response that recognized target cells pulsed with the same p53 peptide, did not generate CTL that could recognize tumor cells presenting endogenous p53 antigen (Erdile et al. (2000) Cancer Immunology Immunotherapy 49 (8): 410-416). Thus, the prior art of record establishes the difficulties in generating therapeutic immune responses against any antigen of interest and further demonstrates the unpredictability that an antigen specific CTL response will be sufficient to protect a host from challenge with the pathogen associated with that antigen.

As to the generation of therapeutic immune responses against latent infectious agents such as HIV, Fox in a review of the "First National Conference on Human Retroviruses and Related Infections" summarizes the conference's central theme as, "no therapy has emerged as a sure winner in the campaign against HIV, not a preventive vaccine nor a therapeutic vaccine nor any of the immune-system-boosting treatments" (Fox (1994) Bio/Technology, 12, 128). Furthermore, Klein et al. in a review of the challenges facing the development of HIV vaccines states, " A fundamental question in HIV vaccine research is what factors correlate strongly with

protective immunity or prevent the progression to AIDS. The answer is still unknown", " The results of studies in animals and humans are inconclusive about what factors correlate with what kinds of protection", and, "The likely composition of a successful HIV vaccine is still unknown, primarily because the factors involved in immunity that must be targeted by the vaccine are still unclear" (Klein et al. (2000) Clinical Therapeutics, Vol. 22 (3), 295-314, see pages 303 and 310 in particular). Thus, the art at the time of filing demonstrates the unpredictability in generating therapeutic or prophylactic immune responses against pathogens, and in particular immunodeficiency viruses such as SIV and HIV, by immunization with nucleic acids.

Therefore, in view of the state of the art of generating therapeutic immune responses at the time of filing, the lack of specific guidance provided by the specification for using DR5 to enhance immune responses, the limitation of the declaratory evidence to a showing that DR5 can enhance CD8+ T cell responses, the art recognized unpredictability in immunizing against any disease by generating a CD8+ T cell response, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 41 recites, "The method of claim 12....". However, claim 12 is directed to a pyrogen-free composition comprising two plasmids and does not recite "a method". As such, the claim is confusing and metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC 102

The rejection of claims 1-3, 6, and 12 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,417,328 (7/9/02), hereafter referred to as Alnemri, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection of record for reasons of record as discussed in detail below..

The applicant reiterates their arguments that Alnemri et al. does not teach the limitation that the plasmid or plasmid compositions are "pyrogen-free", and therefore does not anticipate the claims as amended. In response, Alnemri et al. specifically teaches the pharmaceutical use of plasmids encoding DR5 to treat disease and further teaches that the pharmaceutical composition is "a sterile aqueous solution that contains no materials in addition to the active ingredients and water or physiological saline (Alnemri et al., columns 22-23, particularly column 23, lines 12-20, emphasis added). Thus, while Alnemri et al. does not specifically use the word "pyrogen-free", Alnemri et al. discloses compositions that are sterile and do not contain material other than the active ingredient, i.e. the plasmid encoding DR5, and water or physiological saline. Such a sterile composition is inherently "pyrogen-free". While the applicant further argues that "sterile" does not equal "pyrogen free" and that something can be sterile and yet pyrogenic, this argument is not persuasive as Alnemri et al. clearly teaches that in addition to being sterile the pharmaceutical compositions do not contain material other than the active ingredient and water or physiological saline. Since none of the plasmid itself, water, or physiological saline is pyrogenic, the composition as taught by Alnemri et al. is "pyrogen free".

The applicant further argues that Alnemri et al. only teaches the use of the plasmid encoding DR5 and the immunogen LacZ or the combination of the plasmid encoding DR5 and the plasmid encoding CrmA or Flame *in vitro* and that the teachings for making a sterile aqueous solution in columns 22-23 do not apply to these plasmid(s) as the teachings in columns 22-23 refer to pharmaceutical preparations for the treatment of disease and the Alnemri specification does not teach the administration of immunogens with DR5. In response, the disclosure in column 22 refers to "expressible nucleic acids encoding DR5". The plasmids exemplified in columns 27-28 are in fact expressible nucleic acids. Alnemri et al. does not teach that the expressible nucleic acids only encode DR5. As such, since the Alnemri specification broadly teaches to prepare "expressible nucleic acids encoding DR5" as sterile aqueous solutions that do not contain any material other than the nucleic acid, water or physiological saline, the teachings in column 22 to prepare sterile aqueous solutions of the nucleic acids reads on the particular plasmids disclosed in the examples regardless of whether they were actually used in *in vitro* experiments. Therefore, the rejection of record is maintained.

Claim Rejections - 35 USC § 103

The rejection of claims 1-3, 6, and 12 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,417,328 (7/9/02), hereafter referred to as Alnemri, in view of U.S. Patent No. 5,693,622 (12/2/97), hereafter referred to as Wolff et al. is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection of record for reasons of record as discussed in detail below..

Applicant's arguments regarding the teachings of Alnemri et al. have been addressed in detail below and have not been found persuasive in overcoming the particular teachings of Alnemri et al. Regarding the applicant's argument that the skilled artisan would not be motivated to prepare the plasmids disclosed by Alnemri using the techniques disclosed by Wolff et al. for preparing sterile, pyrogen free plasmids for injection into mammals, it is reiterated that since the Alnemri specification broadly teaches to prepare "expressible nucleic acids encoding DR5" as sterile aqueous solutions that do not contain any material other than the nucleic acid, water or physiological saline, the teachings in column 22 to prepare sterile aqueous solutions of the nucleic acids reads on the particular plasmids disclosed in the examples regardless of whether they were actually used in *in vitro* experiments. Thus, in view of teachings of Alnemri et al. to prepare a sterile pharmaceutical composition comprising a plasmid(s) encoding DR5 for administration to a mammal, and the teachings of Wolff et al. for standard methods of preparing plasmid DNA for in vivo administration, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the standard methods taught by Wolff et al. to prepare the plasmids encoding DR5 and an immunogen taught by Alnemri et al.. Further, based on the standard nature of cesium chloride purification, and the high level of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in producing a pyrogen-free composition containing the plasmid(s) taught by Alnemri et al. using the purification method taught by Wolff et al.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

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